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ORIGINAL ARTICLE

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Clinical assessment of gastric emptying and sensory function utilizing gamma scintigraphy: Establishment of reference intervals for the liquid and solid components of the Nottingham test meal in healthy subjects

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Abstract

Background: Current investigations of stomach function are based on small test meals that do not reliably induce symptoms and analysis techniques that rarely detect clinically relevant dysfunction. This study presents the reference intervals of the modular “Nottingham test meal” (NTM) for assessment of gastric function by gamma scintigraphy (GSc) in a representative population of healthy volunteers (HVs) stratified for age and sex.

Methods: The NTM comprises 400 mL liquid nutrient (0.75 kcal/mL) and an optional solid component (12 solid agar-beads (0 kcal)). Filling and dyspeptic sensations were documented by 100 mm visual analogue scale (VAS). Gamma scintigraphy parameters that describe early and late phase Gastric emptying (GE) were calculated from validated models.

Key Results: Gastric emptying (GE) of the liquid component was measured in 73 HVs (male 34; aged 45±20). The NTM produced normal postprandial fullness (VAS ≥30 in 41/74 subjects). Dyspeptic symptoms were rare (VAS ≥30 in 2/74 subjects). Gastric

Abbreviations: GCV0, Gastric content volume at time 0 minutes (mL); GE, Gastric emptying; GErateT₅₀, Gastric emptying rate at half emptying time (mL/min); GSc, Gastric scintigraphy; GI, Gastrointestinal; HV, Healthy volunteer; Liquid-NTM, Liquid Nottingham test meal; Mixed-NTM, Mixed Nottingham test meal; NTM, Nottingham test meal; T₅₀, Half emptying time.

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emptying half-time with the Liquid- and Solid-component -NTM was median 44 (95% reference interval 28-78) minutes and 162 (144-193) minutes, respectively. Gastric accommodation was assessed by the ratio of the liquid-NTM retained in the proximal:total stomach and by Early phase emptying assessed by gastric volume after completing the meal (GCV0). No consistent effect of anthropometric measures on GE parameters was present.

Conclusions and Inferences: Reference intervals are presented for GSc measurements of gastric motor and sensory function assessed by the NTM. Studies involving patients are required to determine whether the reference interval range offers optimal diagnostic sensitivity and specificity.

KEYWORDS

gamma scintigraphy, gastric emptying, visceral sensitivity

1 | INTRODUCTION

Postprandial dyspeptic symptoms including uncomfortable fullness, early satiety, bloating, heartburn, nausea and abdominal pain affect up to one in five of the general community and are responsible for up to 25% of referrals to out-patient gastroenterology.¹⁻³ Assessment of gastric function is indicated in patients with normal endoscopy that fail to respond to empirical therapy with acid suppression and antiemetics. Gamma scintigraphy (GSc) provides direct measurements of gastric emptying (GE) and is the reference standard.

Currently, the low-fat, "eggbeater" meal is the best-established test meal used with GSc.^{4,5} Using this method, delayed GE can be documented in approximately 40% of patients with functional dyspepsia and up to 75% of patients with chronic unexplained nausea and vomiting.⁶⁻⁸ Severely delayed GE ("gastroparesis" or "gastric failure") is associated with postprandial vomiting, weight loss, poor health status and poor outcome of therapy;⁸⁻¹⁰ however, such cases are rare and studies have not demonstrated an association of abnormal GE with dyspeptic symptoms.^{8,11} Moreover, delayed GE does not consistently predict clinical response to metoclopramide or other prokinetic and antiemetic medications.^{12,13} Thus, there is a clear need for clinical investigations suitable for routine practice that can identify the causes of dyspeptic symptoms and direct effective therapy.¹⁴

We hypothesized that the relatively poor association between dyspeptic symptoms and GE measured by GSc may be due to limitations related to (i) the test meal, (ii) analysis of imaging data and (iii) failure to induce and/or record gastric sensations.

To address the first issue, we developed the modular liquid/solid Nottingham test meal (NTM) which has a higher volume and higher fat content than other, established test meals.^{5,15-17} In validation studies the NTM triggered normal postprandial sensations in healthy subjects and provided reproducible measurements of GE with non-invasive imaging.¹⁸ The second issue with current GSc studies is that analysis is generally limited to a single outcome measurement (e.g., GE half-time

Key Points

- Failure of current investigations to explain the causes of dyspeptic symptoms may be related to small test meals and analysis techniques that rarely detect clinically relevant symptoms.
- This study provides reference intervals for gastric motor and sensory function by gastric scintigraphy for the large liquid/solid Nottingham test meal (NTM).
- Distinct early and late-phases of Gastric emptying (GE) were detected and gastric accommodation was assessed by the ratio of proximal:total filling. The NTM is well tolerated and suitable for use in clinical practice.

[T₅₀], residual volume at 4 h).^{4,5,19} However, most patients with functional dyspepsia report symptoms during gastric filling or immediately after ingestion of the meal and not hours later.²⁰⁻²³ These postprandial symptoms are often related to impaired gastric relaxation ("accommodation") and hypersensitivity;⁹ however, such elements of gastric function are not assessed by current GSc protocols. The distribution of a liquid test meal in the stomach provides one non-invasive measure of accommodation.^{24,25} The effect of accommodation on early- and late-phase GE provides another method to assess this process.^{23,26-30} Both are documented in by the GSc analysis presented here. Additionally, the solid component of the NTM is comprised of agar beads with a known breaking strength. Emptying of this solid component provides an assessment of the mechanical work done by the antral contraction waves (trituration).¹⁹ Finally, gastric sensitivity can be assessed by concurrent reporting of symptoms during gastric filling and emptying using validated scores.³¹ This study presents reference intervals for the assessment of gastric motor and sensory function by GSc for the large, modular NTM.

2 | MATERIALS AND METHODS

2.1 | Participants

Adult healthy volunteers (HVs) aged 18–80 were recruited by advertisement. Subjects were stratified by age and sex so that a minimum of 10 men and women in three age groups (18–40, 41–60, 61–80) completed the Liquid-NTM. A subset of participants also completed the Mixed-NTM (Liquid and Solid components). All subjects underwent the same screening procedures.

At the initial screening visit, participants completed validated questionnaires regarding their health and wellbeing. These included patient health questionnaire (PHQ 12), hospital anxiety and depression questionnaire (HADS) and the EuroQol 5D™ (EQ-5D) quality of life questionnaire.^{32–34} Participants also underwent a physical exam. Those invited to participate had no evidence of current medical problems, no functional gastrointestinal (GI) disease as defined by the Rome III Questionnaire or history of GI disease or surgery (other than appendicitis or hysterectomy). Subjects were excluded if they had a waist circumference of over 100 cm and/or a body mass index (BMI) of less than 18 or over 30, took medication which may affect esophageal or gastric motility for 7 days prior to investigation, had an active eating disorder, vegan diet or allergy to milk protein. They had not participated in another radionuclide study within the previous 3 months or had any contraindication to MRI.

Screening also included a nutrient drink test using the same liquid nutrient (0.75 kcal/mL) with the same nutrient composition as the modular Nottingham test meal (NTM). Participants were required to drink in a standardized and controlled fashion, drinking from a series of beakers containing 40 mL liquid nutrient every minute. During the drinking test, subjects scored satiety, fullness, bloating, heartburn, nausea and epigastric pain at 5 minutes intervals using a 100-mm visual analogue scale. Participants were instructed to cease intake if severe dyspeptic symptoms (VAS score >90 mm) were caused.

The protocol was approved by the NRES Committee East Midlands-Derby 1 and the Nottingham Research Ethics Committee 2. The study was registered at www.ClinicalTrials.gov (NCT01919021). Written informed consent was obtained from each participant. All procedures were performed in Nottingham University Hospital and the University of Nottingham, UK.

2.2 | General procedures

Subjects fasted from midnight and abstained from alcohol and strenuous exercise for 24 hours prior to each study day. Smoking was not permitted during the study. Subjects underwent gastric scintigraphy (GSc) and magnetic resonance imaging (MRI) on separate study days, a minimum of 48 hours apart. Each study including the screening visit was completed within a 4-month period. Magnetic resonance imaging data will be reported in separate publications.

2.2.1 | Blood glucose measurement

Subjects participating in the Mixed-NTM study had capillary blood glucose measurements taken from the ear lobe at baseline (i.e., before

ingestion of MNTM), 30, 60 and 120 minutes post-ingestion of the Mixed-NTM (Optium Xceed™ system, Medisense, Abbott Laboratories Ltd, Berkshire, UK). Before each sample was taken a small amount of rubifacant (Deep heat rub, Mentholatum, UK) was applied to the ear lobe approximately 1–3 minutes prior to the test. The rubifacant was used to improve circulation (“arterialization”) of the capillary bed to ensure more reliable measurements of blood glucose. The rubifacant was removed from the area prior with moist cotton wool or gauze prior to the test. Further, in a subset of 8 HVs participating in the Liquid-NTM a 5 mL venous blood sample and blood glucose measurements were taken at baseline, 30 minutes, 60 minutes and 120 minutes post Liquid-NTM ingestion. Venous cannulas were placed on study mornings prior to ingestion of the test meal. A small amount of blood from each sample was applied to the Optium Xceed™ blood glucose test strips. The average of three measurements from each sample was then recorded.

2.3 | NTM preparation

The Liquid-NTM comprised 400 mL vanilla Fortisip (Nutricia Clinical; Wiltshire, UK) diluted 1:1 with water (300 kcal, 11.6 g fat, 12 g protein, 36.8 g carbohydrates). 5 MBq of the non-absorbable marker Technetium-99m-diethylene-triamine-pentaacetate (Technescan® DTPA [DRN4362], Mallinckrodt Medical B.V., The Netherlands) (Tc-99m-DTPA) was added to the liquid for scintigraphic imaging of the test meal within the stomach and bowel.

The Mixed-NTM contained the same liquid component but with 0.5 MBq of the non-absorbable marker 111-indium chloride. The solid component was labeled with Technetium-99m-MAA (Technescan® LyoMAA [DRN4378]). The solid component of the meal comprised 12 food grade agar beads (11.5 mm in diameter) prepared as originally described by Marciani et al.³⁵ with 1% Agar-Agar (Cuisine-innovation, Dijon, France) and 7.0 g/100 mL barium sulphate (E-Z-Paque; Buckinghamshire, UK Ph Eur 96% w/w) plus 5 MBq Technetium-99m-MAA. The barium was added to the agar beads to ensure that they remained negatively buoyant (i.e., did not float on the meal). The breaking strength of the agar beads was 0.8 N/m² as calculated by a tablet hardness tester (Erweka THB100, Heussentamm, Germany).

2.4 | Study protocol

Radioactive markers were affixed to the subject at the right costal margin, both anteriorly and posteriorly. Subjects stood in front of a large field view Gamma Camera (Nucline X-Ring-R, Mediso, Budapest, Hungary). Anterior and posterior planar images each of 30 s duration were acquired and stored on dedicated nuclear medicine computer system (Hermes Medical Solutions, London, UK).

2.4.1 | Liquid Nottingham test meal (Liquid-NTM)

After baseline imaging, 200 mL of the liquid test meal was ingested from a series of beakers containing 50 mL liquid nutrient over 5 minutes. The subject was then imaged (~5 minutes scan). The remaining 200 mL of the test meal was then given in the same manner so that the entire test meal was consumed over 10 minutes and the subject

imaged again (0 minutes scan). Gastric scintigraphy images were then acquired at 5, 10, 15, 30, 45, 60, 75, 90, 120 minutes. At baseline and after each scan the subjects were asked to score satiety, fullness, bloating, heartburn, nausea and epigastric pain using a previously validated visual analogue scale (VAS 0-100 mm).³¹

2.4.2 | Mixed Nottingham test meal (Mixed-NTM)

The first 200 mL of the liquid test meal was ingested as described above and the subject imaged (~5 minutes scan). The remaining nutrient drink was then given with 12 agar beads swallowed whole (3 beads with every 50 mL beaker).¹⁸ This two-stage methodology allowed the In-111 Cl₃ gamma photon scatter within the Tc-99m channel on the GSc images to be calculated. Imaging continued for 120 minutes as for the liquid meal but with an additional 75- and 115-minute time point. After the 115-minute scan 200 mL of water was given ahead of the final scan at 120 minutes (procedure required for MRI study). Additional scans were performed in a subset of patients at 30-minute intervals until a maximum of 4 hour. Gastric sensation was assessed as for the Liquid-NTM. Note: the data from some of the subjects included in this study has been previously published in pilot studies.¹⁸

2.5 | Analysis

2.5.1 | Liquid-NTM study

Liquid GE begins almost immediately during ingestion and, in HVs, is almost always seen at completion of the test meal.³⁰ To measure this early-phase GE two regions of interest (ROIs) were defined around the labeled meal on the 0 minute scan immediately after completion of the test meal (i) around the stomach only representing the volume of the test meal in the stomach after completion of the meal and (ii) around the stomach and small bowel representing the total volume of the 400 mL test meal. The same process was repeated for all subsequent scans from 5 to 120 minutes. This analysis allows meal volume in the stomach to be expressed not only as a proportion (%) of the total meal volume ingested (applied in current studies⁴) but also as an absolute volume (mL) in the stomach (% gastric meal retention×400 mL) at every point in time. Further, to measure the proportion of the test meal in the proximal and distal stomach a ROI was drawn across the stomach at the angulus from the lesser curvature to the greater curvature thus separating the stomach into its proximal and distal sections. Similarly, to the whole gastric content the absolute volume (mL) of the test meal in the proximal and distal section was calculated. All counts were corrected for background radiation and radioactive decay. The early phase GE is expressed as the postprandial volume immediately after completion of the meal from the V_0 parameter (GCV0) and late phase GE is expressed as GE rate (mL/min) at T_{50} (GErate T_{50}). The early phase GE rate (mL/min) was determined by calculating the remaining volume of the test meal present in the stomach at GCV0 and dividing by the 10 minutes required to dose the meal (Early phase GE rate). The fraction of the NTM in the proximal stomach (proximal/whole) was used to present meal distribution within the stomach.

2.5.2 | Mixed-NTM study

Liquid and solid GE were measured in the same way as the liquid only study. The same ROIs were used to calculate the volumes and percentage of liquid and solid meal in the stomach. The In-111 overlap onto the Tc-99m channel was estimated from the first 200 mL of Tc-99m-labeled Fortisip administered to the subject. The number of counts were then converted to a percentage of the total test meal volume. Due to the low count produced by the 0.5 MBq In-111 Cl₃ label in the mixed meal, the counts were corrected also for background activity (average of anterior and posterior images taken separately assessed at 0 minute). The number of beads present in the stomach at 1 hour and 2 hours is calculated based on the percentage retention of radioactive marker relative to the initial scan after ingestion of beads ("correction" for early GE is not required as this does not occur with the solid beads).

2.6 | Statistical analysis

Demographic results are reported as median with [interquartile range] and Wilcoxon tests were used for between group comparisons. Data analysis of blood glucose measurements was performed using GraphPad Prism version 6.0 (GraphPad Software Inc., La Jolla, CA, USA). Blood glucose measurements are reported as mean with 95% upper and lower (confidence intervals).

Gastric volume data obtained over 120 minutes by GSc were fitted to linear exponential curves with a population-based approach using Stan source code (Data S1).³⁶ Solid (agar bead) emptying data was fitted by a power exponential curve.³⁷ This approach ensures that all curves can be fitted and give regularized coefficient estimates. The reference intervals of the GE parameters were determined by the robust method as given in the Clinical and Laboratory Standards Institute's guideline with Box-Cox transformation and reported as the upper and lower 95% reference intervals (RI) of the population.³⁸ The median was also provided alongside the upper and lower 95% confidence intervals (CI) of the mean. To compute the reference interval for percentage retention of agar bead a logit/antilogit transformation was used to constrain fractions to the range of 0-100%. The initial emptying phase of agar bead emptying was determined by the parameter beta from the power exponential function.³⁷ The absolute percentage of liquid meal emptying calculated from unfitted data is reported as mean with 95% confidence intervals.

Bayesian model averaging was used to determine the effect of anthropometric factors and the addition of agar beads on the liquid GE parameters; a total of 24 combinations of covariates were tested. This method accounts for model uncertainty inherent in the variable selection problem by averaging over the best models in the model class according to the approximate posterior model probabilities.³⁹⁻⁴¹ Inter observer correlation coefficients (ICC) were calculated with SPSS v16.0 (SPSS, Chicago, Illinois, USA). Kendall's tau coefficient was used to determine the correlation between early and late phase emptying and between sensation and gastric volume.

TABLE 1 Demographic, anthropometric and health questionnaire data for healthy volunteers by age and sex reported as the median and [interquartile range]. Wilcoxon tests were used for between group comparisons of sex stratified groups

	n	Age	Height	Weight	BMI	Waist C	PHQ	HADS	EQ-5D
18-40 f	15	21.0 [20.0, 26.0]	1.6 [1.6, 1.7]	59.7 [57.5, 68.2]	22.5 [21.3, 25.0]	79.0 [70.5, 84.5]	2.0 [1.0, 3.0]	4.0 [2.0, 6.0]	90.0 [82.5, 95.0]
41-60 f	11	47.0 [45.0, 52.0]	1.6 [1.6, 1.7]	66.0 [63.5, 68.8]	24.2 [23.6, 26.0]	86.0 [82.0, 88.5]	2.0 [1.5, 3.0]	4.0 [2.2, 5.0]	95.0 [90.0, 100.0]
Over 60 f	13	67.0 [65.0, 75.0]	1.6 [1.6, 1.6]	60.7 [55.9, 71.9]	25.4 [21.0, 27.5]	87.0 [74.0, 95.0]	2.0 [1.0, 6.0]	5.0 [3.0, 7.0]	98.0 [90.0, 100.0]
18-40 m	12	20.5 [20.0, 21.0]	1.8 [1.8, 1.8]	71.0 [66.8, 74.3]	21.8 [20.4, 24.0]	81.0 [78.0, 82.0]	1.0 [0.0, 1.1]	2.5 [1.0, 4.0]	88.8 [78.8, 93.1]
41-60 m	12	47.0 [46.5, 51.2]	1.8 [1.8, 1.8]	81.8 [75.1, 91.0]	26.5 [24.1, 28.1]	94.0 [90.0, 98.0]	1.8 [0.8, 3.0]	4.8 [2.8, 8.0]	88.0 [83.8, 92.8]
Over 60 m	10	67.0 [64.8, 68.0]	1.7 [1.7, 1.8]	76.8 [73.2, 87.0]	25.6 [24.3, 27.6]	92.5 [89.2, 97.5]	2.2 [2.0, 3.8]	7.5 [2.8, 8.9]	90.0 [86.2, 90.0]
P value		<.001	<.001	<.001	.004	<.001	.094	.233	.031

BMI, body mass index; EQ-5D, Euroqol 5D™; f, female; HADS, hospital anxiety and depression score; m, male; n, number; PHQ, patient health questionnaire; P value derived Wilcoxon test comparison of sex stratified groups and Waist C, waist circumference.

3 | RESULTS

3.1 | Participants

In total 91 subjects consented to the studies. Seventeen subjects were excluded during the screening process due to previous history of GI surgery (n=1), current medication which may affect esophageal or gastric function (n=1) and BMI >30 kg/m² (n=15). A total of 74 HVs entered the NTM studies (61 Liquid-NTM, 24 Mixed-NTM). Eleven subjects completed both the Liquid-NTM study and the Mixed-NTM study. Earlier validation studies demonstrated that the solid component of the test meal had a small but significant effect on liquid GE¹⁸ and, therefore, reference intervals of the Liquid-NTM are presented independently from the Mixed-NTM. Measurements of gastric motor and sensory function obtained with the NTM are reproducible and good inter-observer agreements have been reported previously.¹⁸

Demographic, anthropometric and health questionnaire data for all subjects stratified by age and sex are provided in Table 1. A small number had evidence of a psychological disorder (n=4, HADS>11). Self-rated health status was very good-excellent (>75 VAS in EQ-5D) in all subjects. There were no significant differences between the sub groups for either the HADS, PHQ or EQ-5D self-rated questionnaires Table 1. All subjects tolerated the complete 400 mL Liquid-NTM and Mixed-NTM.

3.2 | Measurement of gastric sensation

There was no difference in the sensation of fullness or satiety reported between the two NTM meals ($P=1.0$ and $P=.46$, respectively), as shown in Figure 1. The mean VAS scores and 95% confidence intervals of fullness and satiety are presented in Table S1. At baseline, most subjects reported less than mild fullness (0-30 mm VAS). After completing the 400 mL test meal most subjects reported more than mild but less than moderate fullness (i.e., between >30 but <60 mm VAS). More than mild bloating (>30 mm VAS) was reported by only two subjects. No other dyspeptic symptoms (i.e., nausea, heartburn, pain) were reported as more than mild throughout the study.

3.3 | Blood glucose measurement

Blood glucose measurements were obtained from 32 subjects that ingested the 400 mL liquid nutrient either as part of the Mixed-NTM (24 subjects or Liquid-NTM study (8 subjects) (37 g carbohydrate in NTM). At baseline the fasting blood glucose had a mean of 5.2 (CI 4.9-5.4) mmol/L. At 30 minutes; 7.1 (CI 6.7-7.5) mmol/L, 60 minutes; 5.7 (CI 4.8-6.3) mmol/L and 120 minutes; 4.8 (CI 4.1-5.3) mmol/L post-NTM ingestion. No individual had evidence of impaired glucose tolerance with fasting blood glucose >6 mmol/L or postprandial levels >11 mmol/L.

3.4 | Liquid gastric emptying

Representative images and data from the Liquid-NTM from a HV participant are shown in Figure 2. One subject from the mixed-NTM

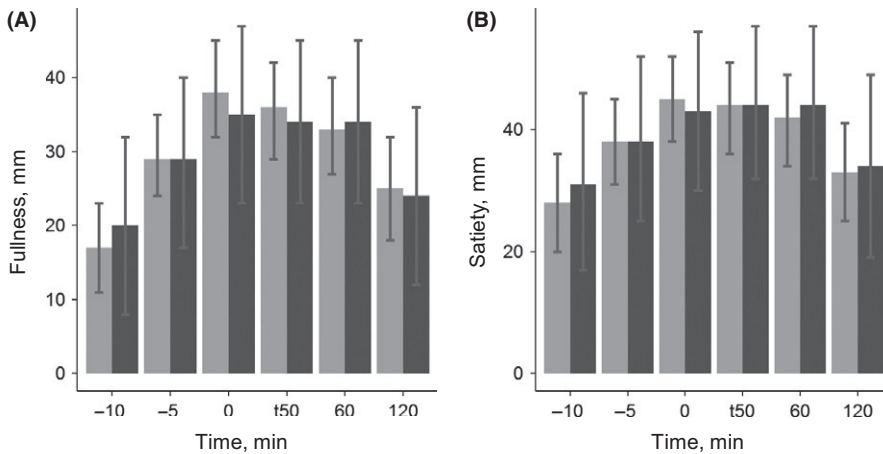


FIGURE 1 Reported visual analogue scores over time after ingestion of Liquid-NTM or Mixed-NTM. The mean and 95% confidence intervals of the mean are provided. (A) Fullness and (B) Satiety. NTM, Nottingham test meal

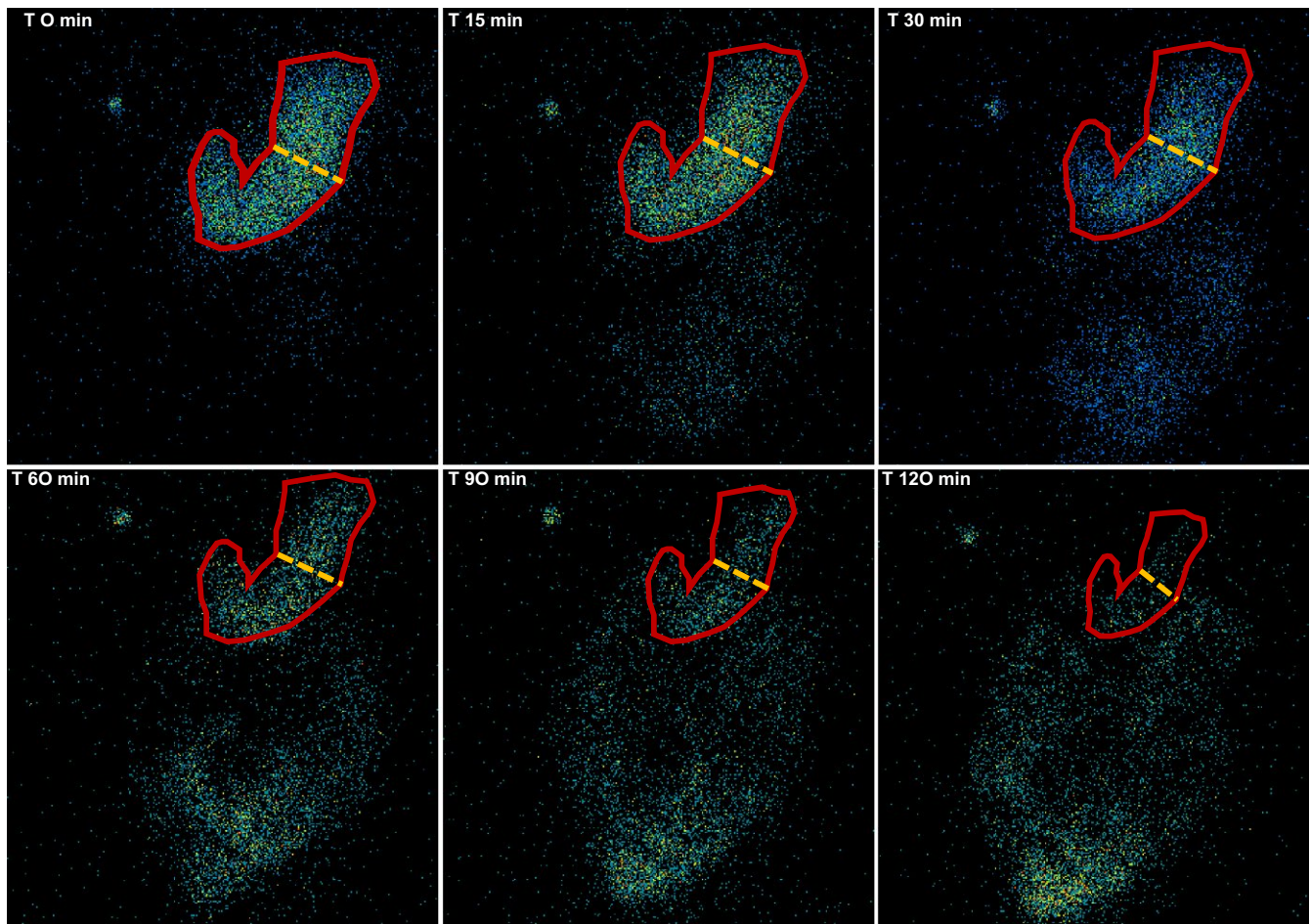


FIGURE 2 Representative images from gamma scintigraphy (anterior view) at time 0, 15, 30, 60, 90 and 120 minutes after Liquid-NTM ingestion. The red line indicates the whole stomach region of interest and the yellow dashed line indicates separation of the stomach into the proximal and distal regions. Liquid-NTM, liquid Nottingham test meal

was excluded due to poor data fit to the model (Bayesian Modeling approach improved upon the previously published single curve model fit where 25% of subjects (6/24) were excluded from the Mixed-NTM study due to poor fit). Gastric emptying measured by GSc followed the same pattern of liquid emptying previously reported.¹⁸ The initial meal volume measured immediately after NTM ingestion was generally less than 400 mL indicating “early phase” GE

that occurs during meal ingestion. Subsequently there is a linear-exponential decrease in gastric meal volume over time (Figure 3). Liquid GE reference intervals are presented in Table 2 for both the Liquid-NTM and the Mixed-NTM. The absolute percentage of liquid gastric retention from the unfitted data is presented in Table S2. As previously reported the agar beads had a small but significant effect on the GE parameters. Bayesian Modeling determined that the T_{50}

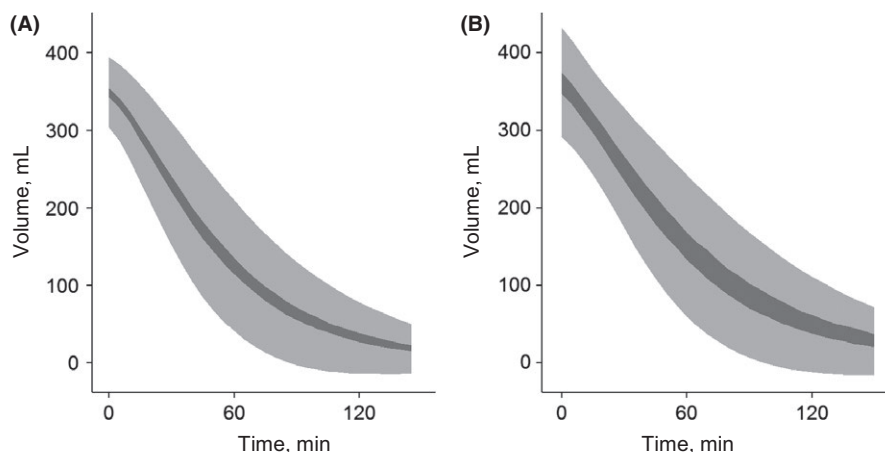


FIGURE 3 Liquid gastric emptying reference intervals of the Liquid-NTM and Mixed-NTM. The outer ribbon represents the 95% reference interval of the population and the inner ribbon represents the bootstrapped 95% confidence interval of the mean. (A) Liquid-NTM and (B) Mixed-NTM. NTM, Nottingham test meal

TABLE 2 Reference intervals of the liquid gastric emptying parameters for the Liquid-NTM and Mixed-NTM

Gastric emptying parameter	NTM	n	Median	95% Confidence interval of the mean	95% Reference interval of the population
GCV0 (mL)	Liquid	61	350	340-353	306-418
GCV0 (mL)	Mixed	23	370	340-374	293-500
Early phase GErate (mL/min)	Liquid	61	4.7	4.3-5.2	2.0-10.5
Early phase GErate (mL/min)	Mixed	23	3.1	1.4-3.7	0.3-41.1
T ₅₀ (minutes)	Liquid	61	44	41-47	28-78
T ₅₀ (minutes)	Mixed	23	52	45-56	29.7-109
GErate _{T₅₀} (mL/min)	Liquid	61	3.8	4.0-3.9	2.4-5.9
GErate _{T₅₀} (mL/min)	Mixed	23	3.1	2.8-3.7	1.6-6.5

Early phase GErate, early phase gastric emptying rate (mL/min); GCV0, gastric content volume (mL); gastric emptying rate GErate_{T₅₀}, gastric emptying rate at T₅₀ (mL/min); n, number of subjects; NTM, Nottingham test meal; and T₅₀, half emptying time (minute) of liquid Fortisip.

was longer by 6 minutes with the Mixed-NTM than the Liquid-NTM, Table S3.

associated with a slower late phase GE rate Figure S1. This interaction was not significant for the Liquid-NTM ($P=.47$).

3.5 | Solid meal gastric emptying

The GE of the solid component of the Mixed-NTM is demonstrated in Figure 4. The reference interval ranges for solid agar bead emptying are presented in Table 3. Solid GE was characterized by an initial, slow emptying phase followed by an essentially linear decrease in volume (Table 3). There was a weak correlation between emptying of solid beads and of the liquid emptying T₅₀ meal ($r=.18$).

3.6 | Interaction of early phase gastric emptying on late phase gastric emptying

There was a moderate negative correlation between early phase GE and late phase GE with the Mixed-NTM (-0.43 , $P=.004$). Thus, the Mixed-NTM demonstrated that a faster early phase GE rate was

3.7 | Meal distribution within the stomach

Image data for GCV0, proximal and distal gastric volumes derived from 10 subjects who ingested the Liquid-NTM were analyzed by three independent observers. The inter-observer agreement for the ROIs for the whole stomach, antrum and fundus were calculated (Table S4). Strong agreement was documented for all measurements. Meal distribution in the stomach was then calculated for all subjects.

The proportion of the liquid meal present in the proximal stomach differed between the Liquid-NTM and Mixed-NTM studies Figure 5. A higher proportion of the liquid meal was present in the proximal stomach of the Mixed-NTM than the Liquid-NTM. Very few agar beads were present in the proximal stomach of the Mixed-NTM because the beads were specifically designed to be negatively buoyant.

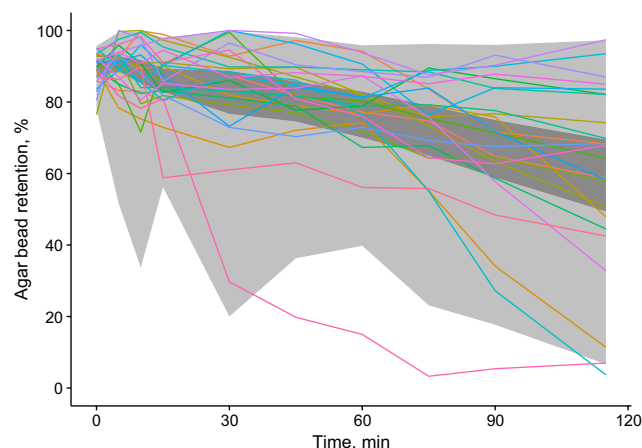


FIGURE 4 Spaghetti plot of percentage agar bead retention per subject over time. The outer ribbon is the approximate 95% reference interval of the population. The inner ribbon demonstrates the bootstrapped 95% confidence intervals of the mean.

3.8 | Relationship of gastric filling and distribution with gastric sensation

The presence of the liquid meal in the proximal stomach of both the Liquid-NTM and Mixed-NTM had no correlation with sensation (fullness, or satiety) at T_0 minute in health Table S5. However, in Figure 5 the VAS scores of fullness and satiety decreases in relation to volume within the proximal stomach.

3.9 | The effect of patient factors on gastric emptying

Bayesian model averaging was used to determine the effect of demographic and anthropometric factors on the GE parameters GCV0, T_{50} and $GE_{rateT_{50}}$. A total of 24 combinations of parameters were tested and the best three alternate models are provided in Table S2. The results indicate that there was no single predictor for both GCV0 and $GE_{rateT_{50}}$. There was a minor effect of age on T_{50} in that for a 10-year increase of age the T_{50} increased by 2 minutes. Similarly, an increase of 1-cm waist circumference was associated with T_{50} increase by 30s. In addition, male sex decreased T_{50} by 7-minute although this predictor had a low probability in the model.

4 | DISCUSSION

This study provides reference intervals for the clinical assessment of gastric motor and sensory function by gastric scintigraphy (GSc) using the large, modular “Nottingham test meal” (NTM). Values are provided for liquid (Table 2) and solid (Table 3) components of the NTM from a large cohort of healthy participants.

4.1 | Gastric emptying

Typical patterns of liquid and solid GE in health were observed.⁴² For the liquid NTM “early phase” emptying commenced during ingestion of the meal and was followed by a “late-phase” linear-exponential reduction in meal volume (Figure 3).¹⁸ Detailed measurements by Magnetic Resonance Imaging (MRI) following ingestion of a liquid test meal have shown that “early phase” GE is driven by volume load alone, whereas “late phase” GE is modulated by volume and calorie load (i.e., neurohormonal feedback).^{23,26-30,43} Further studies have shown increased early phase GE in functional dyspepsia patients with impaired accommodation detected by gastric barostat.²⁶ The same effect was observed also with GSc after ingestion of the 400 mL NTM.²³ In pilot clinical studies rapid early GE after the meal was observed in a proportion of patients with functional dyspepsia and this may indicate the presence of impaired gastric accommodation in this group.²³ Conversely, if symptoms occur in the absence of motor disorders (i.e., abnormal GE) it may be inferred that gastric hypersensitivity is the likely cause of dyspeptic symptoms.

For the solid NTM, GE showed a characteristic initial, slow emptying phase relating to the trituration (breakdown) of the agar beads into smaller particles,¹⁹ followed by an essentially linear pattern of emptying (Figure 4). This provides an objective assessment of the “mechanical work done” by the antral contraction waves in the postprandial period.¹⁹ The retention of solids in the stomach may be more sensitive than abnormal liquid GE for detection of abnormal gastric function in patients with certain conditions (e.g., diabetic gastroparesis).⁴⁴

The NTM is designed to be modular in the sense that the liquid component can be used with or without the non-nutrient solid component. This would be practical because dual-radionuclide studies are relatively expensive and the analysis is complicated due to scatter

Gastric agar bead retention parameter	n	Median	95% Confidence interval of the mean	95% Reference interval of the population
Initial emptying phase (minutes)	23	2	2-3	0-4
Retention 60 minutes (%)	23	81	73-85	36-98
Retention at 120 minutes (%)	23	60	31-68	3-99
T_{50} (minutes)	23	162	144-193	36-303

Initial emptying Phase, time of trituration of agar beads prior to emptying, time of agar bead emptying; Retention 60 minutes (%), Percentage of agar beads retained in the stomach at 60 minutes post ingestion; Retention at 120 minutes, Percentage of agar beads retained in the stomach at 120 minutes post ingestion; T_{50} , half emptying time (minutes) of agar beads.

TABLE 3 Reference interval ranges of solid emptying

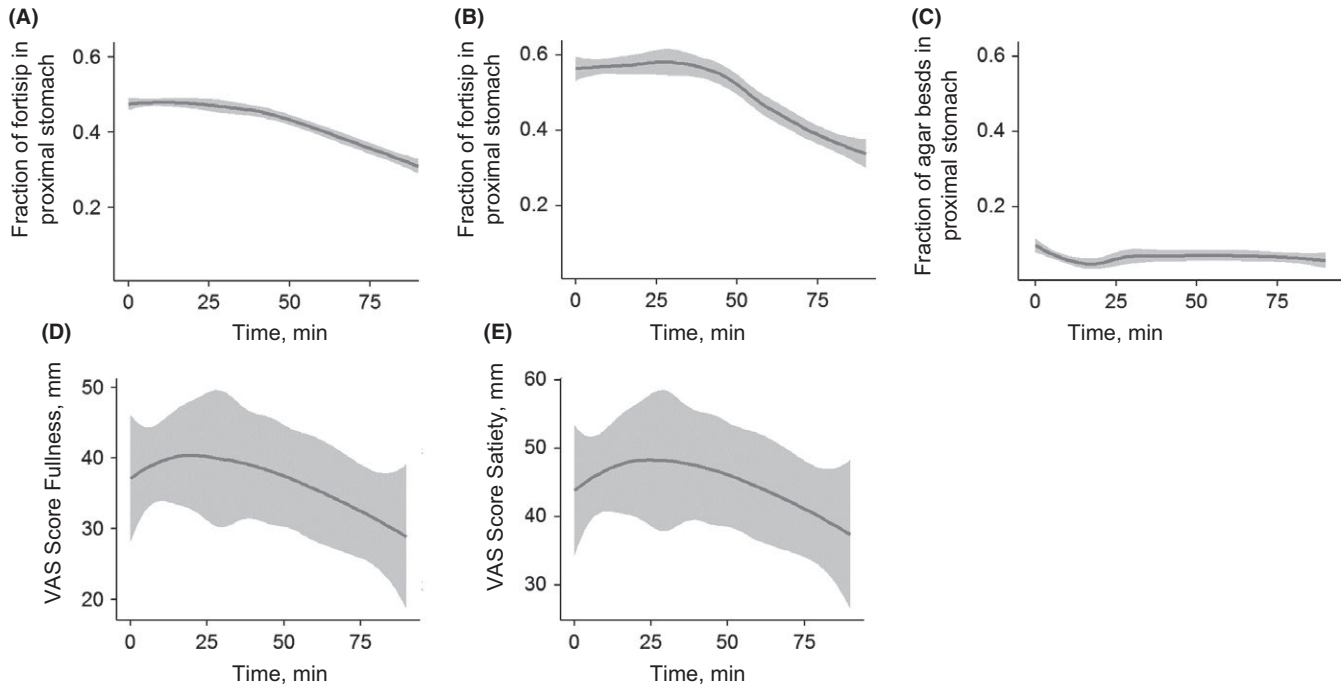


FIGURE 5 Proximal stomach volume fraction of the Nottingham test meal and averaged visual analogue scores of fullness and satiety over time. The confidence intervals are indicated by the grey outer band. (A) Fraction of Liquid-NTM in the proximal stomach, (B) Fraction of liquid component of Mixed-NTM in the proximal stomach, (C) Agar bead component of the Mixed-NTM in the proximal stomach, (D) VAS fullness and (E) VAS satiety. NTM, Nottingham test meal and VAS, visual analogue score

from the In-111 photopeaks (171 keV and 245 keV) onto the Tc99m photopeak (140 keV).¹⁸ The presence of agar beads in the stomach had an effect on early and late phase liquid GE; however, differences in key metrics were small in relation to the inter-individual variation (e.g., <6 minutes difference in T_{50}).

4.2 | Gastric accommodation

The assessment of gastric accommodation is challenging. Barostat measurements provide a direct measurement of gastric volume change at a given pressure; however, this technique is highly invasive and the presence of a large bag in the stomach has effects on GE.²⁶ Less invasive measurements of intra-gastric pressure using high-resolution manometry have been proposed as a surrogate of accommodation; however, pressure change after a 400 mL meal is small (typically <4 mm Hg, at the limit of resolution by current equipment), varies with position relative to the meal and is difficult to interpret without some assessment of volume change.³⁰ Changes in total gastric and meal volume can be measured by non-invasive measurement (e.g., SPECT, MRI) and imaging can be combined with pressure measurement;^{29,30,45} however, these are technically demanding investigations available only in specialist centers. In contrast, GSc provides a simple, non-invasive measurement of radiolabeled meal volume in the stomach. Rapid early-phase GE provides one assessment of gastric accommodation (see above). Impaired gastric accommodation in dyspeptic patients can also alter the distribution of a large, liquid meal from the proximal to the distal stomach.²⁴ This study provides normal values for

the intra-gastric distribution of the large, liquid NTM with the stomach divided into proximal and distal sections using the angulus as an anatomical marker. Interestingly, the presence of the solid agar beads in the distal stomach appeared to effect gastric accommodation. A higher proportion of liquid meal content in the proximal stomach was noted for the Mixed-NTM than in the Liquid-NTM. Additionally, there was a correlation between early- and late-phase emptying with the Mixed-NTM such that fast early phase GE tended to be followed by slow late phase GE. This is likely due to relatively rapid initial delivery of nutrients to the small bowel leading to the rapid release of neurohormonal factors that slow GE to ensure efficient absorption and assimilation of the meal (the so-called small bowel or “ileal brake.”⁴⁶)

4.3 | Gastric sensation

Many studies have shown a linear relation between meal volume filling and gastric filling sensation.^{47,48} The sense of fullness is modulated by various factors including the composition of the meal, with dietary fat known to increase visceral sensitivity more than other macronutrients.⁴⁷⁻⁴⁹ The liquid NTM has a larger volume and higher fat content than most other test meals.^{5,15-17} Consistent with published pilot data,¹⁸ and the results from “nutrient drink tests,”^{50,51} 200 mL liquid nutrient was not sensed by most subjects, whereas 400 mL was sufficient to induce mild-moderate gastric filling sensations. This sensation was maximal shortly after completing the meal and then reduced with gastric volume over the course of the study (Figure 4). Postprandial bloating was only reported by two individuals and no other dyspeptic

symptoms were reported (<30 VAS). At the same time a normal glycemic response was observed in all patients. This confirms that the NTM provides a realistic physiological challenge to gastric function and digestion. Pilot data indicates that this volume can be ingested by >90% of patients but, in this group, the NTM induces not only fullness but also relevant dyspeptic symptoms.²³ The relationship between measurements of gastric motor and sensory function is a key aim of ongoing clinical studies.

4.4 | Effect of age, sex and weight on GE

Consistent with most previous reports,^{4,52-55} there was no clinically relevant effect of demographic factors on early- or late-phase GE for the Liquid- or Solid NTM. We observed a very small increase in T_{50} with age; however, the NTM study excluded children and the very elderly (>80 years) and results could be more pronounced in these groups. Additionally, slightly slower T_{50} was documented in females than males, presumably due to hormonal factors (e.g., progesterone) that likely modulate GE via effects on smooth-muscle function.^{52,56,57} There was also a minor interaction between T_{50} and waist circumference within the healthy range tested. Recently our group reported that GE was slower in patients with clinically stable anorexia nervosa than in healthy subjects or obese patients.⁵⁸ Other studies showed no such findings; however, in all cases, the effects of body weight on GE were small. In summary, we consider that the reference values for the NTM can be applied without adaption for demographic or anthropometric factors.

4.5 | Limitations

This study provides reference intervals for gastric function from a large, representative population of healthy individuals ($n=74$); however, the Clinical Laboratory Standard Institute has recommended a minimum of 120 patients to establish normal values in a system with large inter-individual variation and a large degree of physiological redundancy.³⁸ An alternative approach applied by other, well-established measurements of gastrointestinal physiology such as the Chicago Classification of esophageal motility disorders, is to apply this data alongside patient data to determine thresholds that define not the "normal range," but definitively pathological function.⁵⁹ These studies are in progress and will also establish the utility of the NTM methodology in clinical practice. Further limitations include the relatively slow emptying of the solid component of the NTM. The Mixed-NTM study was limited by practical considerations to 120 minutes in some cases (a subset continued until 240 minutes). In some cases, T_{50} for the solid meal had not been reached within this time. A reliable estimate of GE metrics requires data to be recorded until approximately 50% of the test meal has emptied.⁴ Thus, the imaging schedule for the Mixed-NTM may have to be extended beyond 120-minute for a reliable estimate of solid GE to be obtained. Comparison of GSc and MRI data in pilot studies demonstrated that, although breakdown (trituration) of agar beads almost always occurs before emptying,^{18,35} the association

between the time to 50% breakdown of beads and 50% emptying of the solid agar beads is weak. This confirms that distinct processes are required for trituration and emptying of solids. It follows that slow solid GE could be due either to impaired gastric contractility or pyloric function. The cause of slow solid GE could be further investigated by routine assessment of antral contraction wave activity during GSc. This technique has been validated against manometry⁶⁰ and abnormal contractile activity has been reported in both diabetic gastroparesis and functional dyspepsia.^{61,62} It should be noted that a somewhat larger dose of radioactive marker is required for these measurements. Finally, the NTM (Liquid or Mixed) is not typical of a normal meal. Most meals are heterogeneous with liquid and solid components that empty at different rates and issues such as mastication rates or layering of fats within the stomach can have important effects on gastric emptying.⁶³⁻⁶⁵ The use of homogenous liquid and solid components for the NTM limits many of these, potential, confounding factors and allows independent assessment of various gastric functions; however, as in many other clinical investigations, although simplification makes the test easier to perform and analyze it also makes it less physiological.

4.6 | Potential application in clinical practice

Gastric function was measured using standard GSc technology without the need for specialized equipment. The time required to complete GSc with the liquid NTM is 2 hours which is less than that employing other radiolabeled test meals.^{4,16,53} Gastric volume data was fitted and analyzed using open-access software (Menne Biomed, Tübingen, Germany). This is optimal with regards to data fitting; however, standard imaging analysis can be applied.⁶⁶ Finally, the NTM is inexpensive, simple to prepare and easy to administer. It is also suitable for use with those special dietary requirements (e.g., vegetarians) and does not contain lactose, gluten, eggs or other food substances linked with food intolerance or allergy. These attributes of the NTM ensure that there should be few barriers to implementation.

In upcoming publications based on data obtained by the NTM in routine clinical practice, we will assess whether non-invasive imaging of gastric function can identify the causes of symptoms in patients with functional dyspepsia, gastroparesis and related conditions. As in other areas of medicine, it is likely that definition of clinical phenotypes based on objective measurement is a key step to effective and specific treatment of these challenging conditions.

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AUTHOR CONTRIBUTION

The authors' responsibilities were as follows: HLP, ET, and EB were involved in planning and performance of study, data collection, interpretation and analysis. CLH and DM data interpretation and analysis; LM and AP were involved in planning of study and data interpretation;

MF developed the study concept and protocol, and MF directed data interpretation and analysis. HLP drafted and MF wrote the manuscript.

DISCLOSURE

The authors report no conflict of interest.

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SUPPORTING INFORMATION

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